



**NTP**  
National Toxicology Program

# Research Concept: $\beta$ -*N*-Methylamino-L-alanine

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NIEHS/NTP

NTP Board of Scientific Counselors Meeting

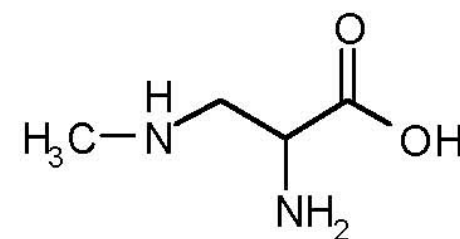
November 20-21, 2008





## $\beta$ -N-Methylamino-L-alanine (L-BMAA)

- Nominated by NIEHS based on:
  - Potential for widespread human exposure
  - Evidence of neurotoxicity in animals
- Produced by cyanobacteria (blue-green algae):
  - Found in marine, freshwater, and terrestrial environments
- Potential human exposure to L-BMAA:
  - Algae blooms
  - Bioconcentrated in plants and animals consumed as food
  - May be present in some blue-green algae dietary supplements





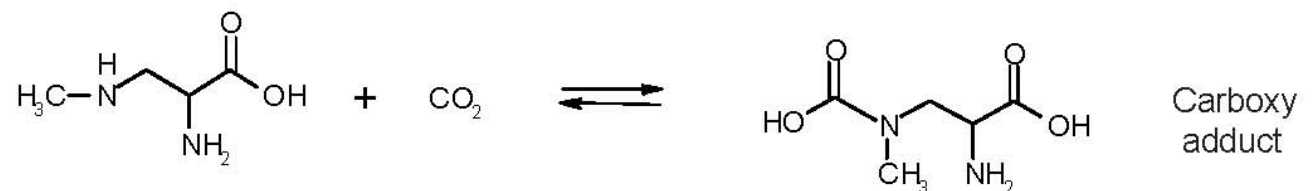
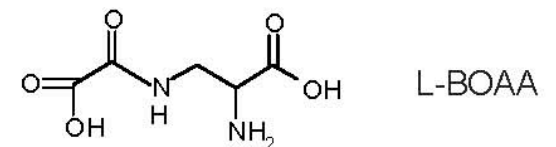
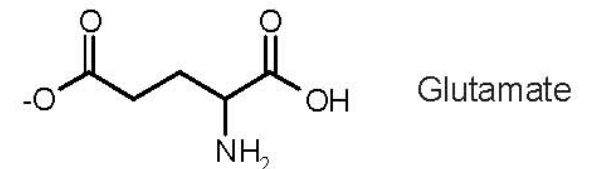
## Toxicity

- Toxic to motor neurons *in vitro*
- Causes neurotoxicity in animals at high doses:
  - Chickens (inability to stand)
  - Rats and mice (weakness and convulsions)
  - Monkeys (tremor, weakness, behavioral changes, degeneration of motor neurons)
- Neurotoxicity in humans linked to L-BMAA exposure?
  - Specific population: High incidence of amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia complex (PDC) on Guam linked to exposure to L-BMAA in cultural diet
    - ALS: Progressive limb weakness and degeneration of motor neurons
    - PDC: Tremor, slowed movement, rigidity, cognitive dysfunctions
  - General population? L-BMAA detected in brain tissue of some Alzheimer's patients



## Mechanism of Action

- Acute toxicity: Glutamate receptor agonist
  - Glutamate is the predominant excitatory neurotransmitter in vertebrates. Excess receptor ligand = excitotoxicity
  - Beta-*N*-oxalylamino-L-alanine (L-BOAA) activates glutamate receptors and is linked to neurotoxicity in humans
- L-BMAA is activated by carboxylation:



- Proposed mechanism of latent and progressive neurotoxicity in humans:
  - L-BMAA incorporated into proteins of brain and other neural tissues
  - Damages neuroproteins and/or serves as a reservoir for continuous low-level exposure of the active metabolite to motor neurons



## Data Gaps and Key Issues

- Extent of exposure to humans is uncertain
  - Environment?
  - Dietary Supplements?
- Risk to humans following exposure is uncertain
  - L-BMAA may be more potent than previously indicated
    - Damages specific neurons and potentiates neuronal injury at  $\mu\text{M}$  concentrations
  - The fate of L-BMAA has not been adequately characterized in an animal model
    - Data describing accumulation, protein interactions, and persistence in tissues are needed to assess the proposed mechanism of toxicity in humans



## Proposed Research Program

- Goal: To further the toxicological characterization of L-BMAA
- Specific Aim 1: Conduct metabolism and disposition (ADME) studies of  $^{14}\text{C}$ -labeled L-BMAA in rodents
  - Quantitate internal dose
  - Determine extent and nature of interaction with proteins
  - Determine elimination kinetics
- Specific Aim 2: Further assess the biological activity of L-BMAA
  - Use *in vitro* techniques and compare with other neurotoxins
- Specific Aim 3: Analyze for the presence of L-BMAA in samples of blue-green algae supplements



## Significance and Outcome

- These studies would:
  - Provide data for assessing the proposed mechanism of neurotoxicity
  - Provide additional information about biological activity
  - Determine if dietary supplements are a source of exposure
- These data would be used for:
  - Assessing risk of exposure
  - Public health guidance
  - Determining the need for toxicity testing



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## Questions and Comments